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STATISTICAL APPROACHES TO POST-MARKET SURVEILLANCE AND DEVICE SAFETY IN MEDICAL DEVICE INDUSTRIES

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ABSTRACT

A foundation of contemporary healthcare system is medical devices (MDs). Manufacturing, marketing, and use must be controlled at all levels due to their relevance in everyday medical practice. Utilising the traceability of MD measurements, a systematic evidence-based conformance evaluation of MDs during PMS has the potential to improve diagnostic and treatment accuracy. Following their authorisation for sale, PMS is essential for ensuring the continued efficacy and safety of medical devices. The effectiveness and dependability of medical devices rely heavily on post-market monitoring (PMS). The purpose of this research is to examine how Change Point Analysis (CPA) may be used to improve PMS by spotting changes in adverse event patterns that are statistically significant. By applying CPA to twelve years' worth of monthly neurostimulator adverse event data from the FDA MAUDE database (2000–2012), we were able to identify change points when there were noticeable alterations in the mean and variance. The Cumulative Sum Control Chart (CUSUM) method was utilised to identify changes in the mean, while bootstrapping techniques validated the statistical significance of these change points ($p \leq 0.05$). Key findings included identifying major events such as battery issues in June 2008 and expanded device warnings in May 2011, both linked to increases in adverse event reports. This analysis segmented the dataset into pre- and post-change point intervals, enabling focused evaluation of adverse event trends. The results underscore CPA's effectiveness in detecting temporal patterns, improving PMS practices, and streamlining regulatory processes to enhance medical device safety. This study highlights the potential for CPA to scale and integrate larger datasets for more complex analyses in future PMS applications.

KEYWORDS: Medical devices (MDs), Post-Market Surveillance, Change Point Analysis (CPA), Cumulative Sum Control Chart (CUSUM), FDA MAUDE database.

1. INTRODUCTION

Nowadays, MDs form the backbone of healthcare. They are highly controlled in manufacture, marketing, and use on a worldwide and national scale due to their considerable importance in human health maintenance. Manufacturers oversee the entire process, while authorised third parties verify conformity and approve commercialisation. The aggregation of data over time removes useful information from the timeline. Finding patterns or shifts in a product's performance over time may be challenging [1]. Directives, legislation, and international standards define and specify the criteria for classifying MD-related activities as either pre-market procedures (PMS) or post-market procedures. For example, the Medical Device Directives (MDD) have established pre-market and PMS procedures in the EU since 1992, and the Medical Device Regulation (MDR) has recently amended these directives[2].

From the initial concept to the final product, medical device manufacturing and PMS are all outlined in the rules and regulations (Figure 1). Worldwide norms have been established to facilitate the execution of rules and regulations. For example, in order to prove that they can reliably meet customer and regulatory demands for MDs

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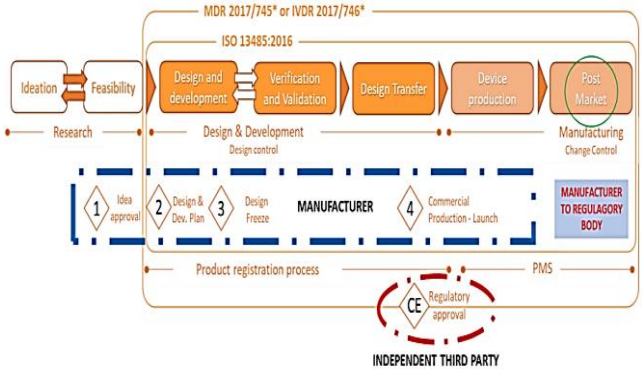
and related services during the pre-market phase, manufacturers are required to adhere to the ISO 13485 standard[3].

Functionality, safety, and performance of MDs must be designed throughout development to meet various requirements outlined in various international standards, including basic safety, electro compatibility, biocompatibility, environmental protection, and many more [4]. Producer and product compliance with environmental, health, and safety regulations are examined throughout the certification process. In the EU, the CE mark is issued by European Notified Bodies, which assess product compliance before they are placed on the market. Similar methodologies are used in the US, where the FDA defines pre-market and post-marketing processes and checks compliance with regulations. The ISO 13485 accreditation proves conformity with regulatory standards in the MENA area.

The SFDA has been in charge of the market via MDIR since 2008, and the UAE and Saudi Arabia (the two most developed nations in the area) both have strong laws for MD. The UAE's Ministry of Health is responsible for medical devices based on the IMDRF and EU Medical Devices Directives[5]. Medical devices (MDs) are manufactured and marketed according to international standards, with various markings utilised to demonstrate compliance with health, safety, and environmental norms.



Medical device process – from idea to market (pre-market process)
PMS is a set of processes utilised to track device performance in healthcare facilities. Despite standardised premarket processes, MDs can still cause errors that lead to patient injury or death. Differences in management strategies, such as preventive services and surveillance, suggest potential difficulties with current PMS methods. The figure depicts the medical device process[6].

Motivation and contribution
The rapid growth and adoption of medical devices in healthcare have brought significant advancements, but they also raise critical concerns about device safety and reliability. Despite rigorous pre-market evaluations, post-market surveillance (PMS) is crucial for identifying unforeseen issues that emerge during real-world usage. Traditional methods of adverse event analysis often struggle to detect subtle or emerging trends in large datasets. This gap motivated the exploration of data-driven, statistically robust methodologies like CPA to improve a detection and understanding of adverse event patterns. CPA's ability to pinpoint significant shifts in trends offers a proactive approach to enhancing medical device safety, enabling earlier interventions and better regulatory oversight. The following research contribution of this paper:

- This study pioneers an employ of CPA as a novel approach to detecting shifts in adverse event data related to medical devices, marking a significant advancement over traditional methods of analysis.
- The research applies CPA specifically to neurostimulator devices, a complex category of medical devices, offering valuable insights into their safety profiles and identifying critical points of change in adverse event trends.
- The study creates a robust, data-driven framework for performing post-market surveillance, using CPA to identify and understand temporal patterns in adverse events, ultimately contributing to improved patient safety.

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- By applying CPA, this work demonstrates how shifts in adverse event trends can be detected early, enabling proactive measures in medical device regulation and potentially preventing larger safety issues before they manifest.
- The technique given in the paper is applicable to a broad variety of medical devices rather than only neurostimulators. This makes it a flexible tool for enhancing the safety of medical devices in the healthcare business as a whole.

Structure of the paper

The following paper are organised as: Section II provide the literature review on medical business for post-market surveillance, Section III discussed proposed methodology with Statistical approaches, Section IV provide the results analysis of Statistical approaches, Section V conclude the paper with conclusion and future scope.

2. LITERATURE REVIEW

In this study, an analysis of the available literature on statistical approaches in the medical business for post-market surveillance after guaranteeing the safety of medical devices is presented on the basis of the findings. Table I that provides a summary of the literature review that was utilised in this study is presented at the very end of the document.

In this study, Botsis et al. (2016) created a DSE for the US FDA medical specialists. 2 integrated systems are part of the DSE: PANACEA and ETHER. Both VAERS and FAERS are systems that medical professionals use to analyse reports of adverse events that have been reported to the Food and Drug Administration. In order to illustrate the DSE's architecture and key features, they provide four use cases: locating missing cases in a case series, detecting duplicate case reports, retrieving cases for a case series analysis, and community detection signal identification and characterisation. They then analyse how these features could be useful in signal management[7].

In this research, Kulldorff and Silva (2017) In situations when it holds off on rejecting a null hypothesis until a certain amount of events have been observed, they examine continuous sequential monitoring. Additionally, they assess delayed-start continuous sequential analysis until a certain sample size is reached. The CDC Vaccine Safety Datalink initiative was the first of its kind to use post-market vaccine safety monitoring in near real-time, allowing for the quick identification of adverse events. While doing weekly analyses, researchers employ continuous sequential techniques to analyse the data almost constantly while maintaining the right overall alpha level. Continuous sequential monitoring allows for the rejection of the null hypothesis with as little as two unfavourable events[8].

In this research, Madigan et al. (2012) lay out statistical procedures for analysing data after approval in an effort to spot medication safety issues in a flash. Given the enormous complexity of the data and the potential future integration of diverse sources of information, Bayesian techniques seem to be particularly valuable. The US FDA and similar agencies have developed detailed, multi-year procedures to ensure the safety and efficacy of new pharmaceuticals. Still, several previously authorised medications have had their sales halted due to severe, even deadly, adverse effects in recent years[9].

This study, Zippel and Bohnet-Joschko (2017) investigated the current status of post-market instrument utilisation in the German MD sector by conducting a nationwide online poll in Q2/2014. The return rate was 36%, and we got 118 complete data sets. Makers of medical equipment spanning all risk categories were surveyed, and their sizes varied. The post-market instruments that were most often mentioned were those that dealt with quality management, production monitoring, literature_observation, regulatory_vigilance_systems, customer_knowledge_management, and market_observation. On the other hand, health services research and post-market clinical follow-up were not as commonly used for product monitoring, and there were notable differences in an intensity of their use by risk class of medical device production. There was hardly any correlation between the magnitude of the tools used and a size of a company. The legislative and regulatory framework relies on device monitoring to detect safety concerns associated with devices, and the results may help advance this system[10].

This research, Vlachos, Kalivas and Panou-Diamandi (2003) proposes a safe and effective electronic post-market surveillance system that meets international standards for statistical analysis, therefore resolving the

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aforementioned issue. Healthcare facilities install a PMS application, while suppliers and manufacturers set up a PMS application. These components make up the system. Important features of PMS systems used to manage PMS Reports and Responses include user-friendly interfaces, interoperability, and different implementations depending on performance and cost requirements. All messages are sent and received in XML format, and the security is based on public-private key cryptography. Multiple users conducted systematic evaluations of the system, and all of them were pleased with its performance and useful features[11].

This study, Chaudhry et al. (2018) investigated Australia's rules on post-purchase monitoring. We provide fog-based POST-market-Surveillance-of-Devices (POST-CODE) middleware that manufacturers may use to get operational facts (without including patient privacy data, of course) about their devices. With the POSTCODE in place, manufacturers will have a better way to keep tabs on how their products are doing. The ownership and control of devices after sale, as well as software upgrades, remain unclear. Once connected to HIS, these devices function as FDA-approved black boxes that only a manufacturer can encrypt, patch, or update[12].

TABLE I. SUMMARY OF THE LITERATURE REVIEW

STUDY	METHODOLOGY	DATASET	LIMITATIONS	RESULTS	FUTURE SCOPE
[7]	Development of two integrated systems (ETHER and PANACEA) for medical experts, aimed at assisting with the VAERS and FAERS data	VAERS, FAERS	Limited to signal management process; specific to FDA experts	Contributed to the signal management process by identifying missing cases, duplicate reports, and aiding in case series analysis	Expanding DSE's application to other adverse event datasets, improving detection of adverse event signals
[8]	Evaluates continuous sequential monitoring methods with critical values, statistical power, and time to signal for vaccine safety monitoring	CDC Vaccine Safety Datalink	Delay in monitoring initiation, logistical constraints on sample size	Demonstrated power increase and reduced expected time to signal while maintaining alpha level; allows early rejection of null hypothesis	Expanding real-time monitoring for broader vaccine safety applications, exploring different monitoring thresholds
[9]	Explores Bayesian statistical methods for detecting drug safety issues post-approval	Post-approval drug data (FDA)	High dimensionality; data from multiple sources may pose challenges	Found Bayesian methods effective for detecting drug safety problems and incorporating diverse data sources	Further development of Bayesian approaches to handle large-scale, multi-source data for drug safety monitoring
[10]	Nationwide survey to explore the use of post-market instruments in the German medical device sector	Survey data from 118 medical device manufacturers	Limited sample size and regional focus (Germany)	Identified key post-market instruments used in device safety monitoring; differences in usage by risk class	Expanding to a larger, international dataset, and deeper analysis of post-market instrument effectiveness
[11]	Development of an electronic PMS system for managing reports and responses; uses XML and public-private key cryptography for security	Post-market surveillance reports	Security and interoperability challenges	The system was effective, efficient, and secure for managing PMS reports and responses	Further development to handle a wider range of medical devices, enhance system scalability and security features
[12]	Development of a fog-based middleware (POST-CODE) to enhance post-sale surveillance of medical devices by providing operational details (excluding private patient data) to manufacturers. Focuses on improving device security, performance monitoring, and device traceability	Operational data from medical devices (excluding private patient data)	Lack of clarity on post-sale ownership and device management; limited focus on device software updates; depends on integration with Healthcare Information Systems (HIS)	POST-CODE enhances device security, enables monitoring and performance upgrades, and builds partnerships between manufacturers and healthcare facilitators. It allows devices to be traceable and malfunctions to be identified.	Expanding POST-CODE's capabilities to include more comprehensive monitoring of device software updates, and addressing ownership and management issues. Exploring wider adoption and integration into HIS and enhancing partnerships between manufacturers and healthcare providers.

3. METHDOLOGY

This statistical research is designed to explore how Change Point research (CPA) may be used to improve medical device PMS. The identification of statistically significant alterations in the patterns of unfavourable occurrences fulfils this objective. This research employs data on adverse occurrences sourced from the FDA-administered MAUDE database. The study's data was gathered monthly over a twelve-year period, from 2000 to 2012, with a primary focus on neurostimulators. Change points in the time-series data were identified and pinpointed through the application of CPA. It was determined that these transition points aligned with occurrences where statistical measures, such as the mean or variance, exhibited substantial changes compared to their prior values. The CUSUM method was utilised to identify alterations in the mean. Notable incidences, such as battery problems in June 2008

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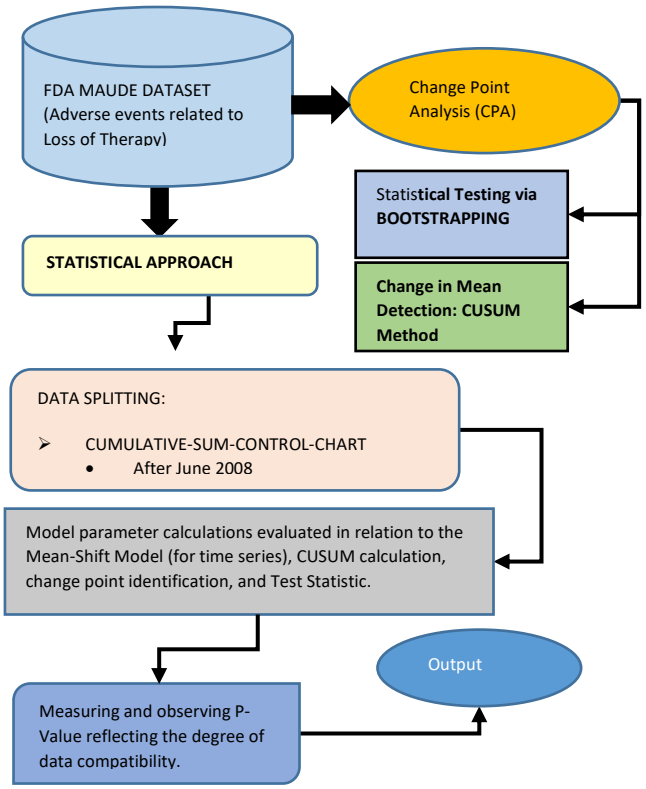
and an upgraded device warning in May 2011, both linked to an increase in adverse event reports, were more easily discernible thanks to these approaches, which enabled the identification of significant occurrences. Executing this procedure required numerous distinct processes. The raw data on adverse occurrences were initially included into a time-series dataset. This signified the initiation of the process. To ensure data consistency, it was essential to detect and correct instances of underreporting during the preprocessing stages. This was performed to guarantee the precision of the data. Subsequently, iterative approaches were utilised within the CPA framework to compute cumulative sums for mean shifts. Subsequent to permutation testing and bootstrapping, these totals were later validated by statistical analysis. The identification of change sites was achieved by examining the most significant variation in cumulative amounts. This analysis was further validated by the computation of p-values, intended to evaluate the level of significance (≤ 0.05). After identifying change points, the next process entails splitting the dataset, which was previously divided according to each pertinent time frame. This was performed to enable focused analysis. This segmentation seeks to provide a targeted analysis of adverse event patterns happening prior to and subsequent to the transition points. This study's results will elucidate the factors that affect the alterations. The utilisation of Critical Path Analysis (CPA) in conjunction with statistical validation offers a powerful method for identifying and evaluating temporal trends in adverse events. The CPA proficiently finds substantial improvements, enhances PMS practices, and streamlines regulatory processes to elevate a safety of MD, as demonstrated by a finding of this study, which validate the effectiveness of the CPA. This technology is anticipated to scale in the future, allowing it to integrate more extensive information and attain more analytical complexity. Figure 2 depicts the proposed methodology flowchart.



Proposed Methodology Flowchart

Data Collection

Counted adverse events associated with treatment discontinuation once per month using data acquired from a single neurostimulator in the FDA's MAUDE database. Many other things may go wrong with treatment, such as a dead battery, an infection, too much stimulation, etc. Years 2000 to 2012 were covered by the data. Treatment loss numbers for each month of the study period are shown in Figure 3.

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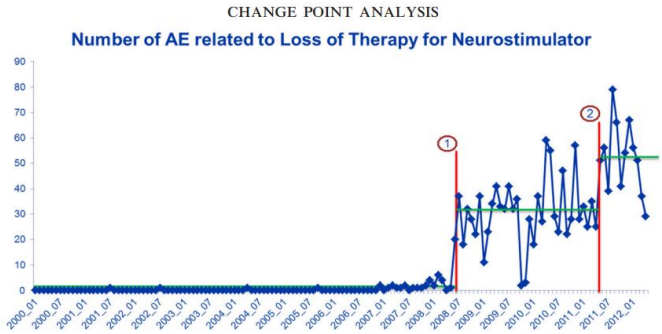

The time series of number of loss of therapy for neurostimulator and their detected change points. AE, adverse event

Statistical Approach

This research employs a statistical methodology centered on CPA, a technique utilised to identify significant alterations in the statistical characteristics (mean) of time-series data concerning adverse occurrences associated with medical equipment. CPA is employed to identify critical points where shifts occur in trends, enabling focused post-market surveillance (PMS) analysis. Both methods were validated using bootstrapping, where random permutations of residuals were tested to construct null distributions. Statistical significance was determined employing p-values($p<0.05$) to confirm the reliability of detected change points. This approach allowed the identification of key shifts in adverse events, such as those in June 2008 (linked to battery failures) and May 2011 (associated with expanded device indications), providing critical insights for PMS. CPA's ability to pinpoint changes in

Change Point Analysis (Cpa) Framework

CPA identifies time points where statistical properties (mean or variance) of the observed time-series data change. The methods of change-point analysis, including CUSUM charts and bootstrap rank statistics, are shown here as proposed by [13]. In this research for Statistical Approach for Post-Market Surveillance and Device Safety in Medical device industries mainly used:

- Change in Mean (CUSUM method)

In order to grasp the crucial data, CPA has been a useful technique. One of a best ways to find out whether there are major shifts in the averages or standard deviations of a set of data points is to utilise change point analysis. It is possible that the identified modification points can provide useful information for post-market review of medical devices [14]. An iterative method divides the dataset into sub-datasets with distinct means, and a recursive algorithm finds many changes using change-point analysis. The best course of action is found by minimising the number of false positive changes via a backward elimination strategy; this approach generates a sequence of predicted change points with varying confidence levels. Time-series data was analysed using CPA to spot changes and patterns. Two primary methods were used. Here are the algorithms for change point analysis:

Let S0, S1,..., Sn represent the total of all points in a time series, and let x1, x2,..., xn represent n data points. There are three stages to apply to the original dataset in order to calculate change-point analysis D0 = {X1,⋯,Xn} ofsize n ($n0 = |\mathcal{D}0|$). Eq. 1 forms a mean $\bar{x}$ of the variables x1, x2,..., xn.

$$\bar{x} = \frac{x1+x2+\cdots.Xn}{n} \qquad (1)$$

At the very beginning, the total will always be zero[15]. That being the case, let S0=0, or set it equal to zero. Afterwards, Eq 2 does the following calculations on Si:

$$Si = Si-1 + (xi - \bar{x}), i = 1, 2, 3, \ldots . n \qquad (2)$$

It is necessary to estimate the size of the changes in order to draw a border for the chart before doing bootstrap analysis. The calculation is Eq 3:

$$S^{t}\text{diff}\, i = \max(i = 0, \cdots, n)Si - \min(i = 0, \cdots, n)Si = Smax - Smin \qquad (3)$$

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It is possible to build CUSUM for both rational subgroups and individual observations. The situation involving singular observations is first examined.

Consider xi to be the process's "ith" observation. When the process is controlled, a normal distribution is followed by xi, where σ is the standard deviation and 0 is the mean, which may be either known or estimated. At times, the goal value for the quality feature X is considered to be μ0. The tabular CUSUM is effective because it adds up a deviation by μ0 thaisre positive (with one statistic C +) and negative (with another statistic C-) relative to the aim. One sided upper CUSUM is the statistical measure C +, whereas one sided lower CUSUM is C -. Their respective values are Eq 4 and 5.

$$Ci^{+} = \max [\, 0, xi - (\mu 0 + k) + C(i-1) \,] \quad (4)$$
$$Ci^{-} = \max [\, 0, (\mu 0 - k) - xi + C(i-1) \,] \quad (5)$$

with the starting value Ci + = Ci - = 0. The value of k, which is frequently selected midway among a goal μ0 and a shift of mean that one is interested in detecting, is referred to as the reference or allowed value. Thus Eq 6,

$$k = \frac{1}{2}.|\, \mu 1 - \mu 0 \,| \quad (6)$$

Deviations from the goal value μ0 that exceed k are added up by the CUSUM values Ci + and Ci -. The process is considered to be uncontrolled if any of these two variablesare beyond the decision interval H. If the process standard deviation is five times σ, then H is a suitable number. Here, H = h * σ and K = k * σ are parameters of the CUSUM.

Statistical Testing Via Bootstrapping

Bootstrapping is a popular method in statistics and economics, involving data gathering, analysis, summarisation, and statistical inference. Modern computer facilities enable efficient, rapid, and flexible application with minimal statistical assumptions, making confidence intervals feasible and enhancing estimating efficiency without adding computing weight[16]. After determining the amount of change, a bootstrap analysis is run N times onD0. A following is the execution of a single bootstrap:

- In a bootstrap dataset Dl of size n, the time series data points from dataset D0 are represented as 'xj', where j = 1, 2, 3,..., n. Sampling without replacement (SWOR) is the process that randomly rearranges the initial n values to create this dataset.
- 'Sj' is the definition of the bootstrap CUSUM, which is calculated using a comparable procedure that is based on a bootstrap sample.

Eq 7 is used to compute the amount of change for a bootstrap CUSUM:

$$Sdiff\, j = \max (j = 0, \cdots, n) Sj - \min (j = 0, \cdots, n) Sj = Smax - Smin \quad (7)$$

Next, the number of bootstraps is determined when an original magnitude of change is greater than a magnitude of change of bootstrap CUSUM, denoted as $Sdiff\ i > Sdiff\ j$[17]

L et N is a total number of bootstrap samples, and K is a total number of bootstraps that have $Sdiff\ i > Sdiff\ j$. Eq 8 is used to establish the % confidence level that a change has happened.

$$CL = \frac{\sum_{i=1}^{N} I(s^{i}diff > s^{j}diff)}{N} \times 100 = \frac{K}{N} \times 100 \quad (8)$$

The outcome of bootstrapping is a technique that does not rely on distributions and relies on the solitary premise of an independent error structure. When the data points are scattered as follows in Eq 9, we have an independent error structure:

$$xi = mi + ei \quad (9)$$

where mi represents a mean at time 'i'. With a few exceptions known as change points, the normal value of i is mi - 1. At the same time, 'ei' is a normally distributed, identically distributed, and independently distributed random error that is associated with an 'i-th' value. A detection of a change allows one to make an estimate as to when a change happened. Here is the formula for calculating the CUSUM estimator, a kindof estimator. So, let's say'm' is such that Eq equals 10.

$$|\, Sm \,| = \max (i = 0, \cdots, n) |\, Si \,| \quad (10)$$

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In this case, "Sm" is the CUSUM chart point that is furthest from zero, while points m and m+1 estimate the points before and after the modification, respectively. In this research after decide if the detected change point is significant, bootstrapping is used:

- Residuals are randomly permuted multiple times (e.g., 1000 times).
- For each permuted dataset, 'Sdiff' is recalculated to form the null distribution.

A p-value is a fraction of permuted 'Sdiff' values that are greater than the 'Sdiff' that was observed from the information that was first collected. Following the completion of this step, a CUSUM plot is plotted, in which a sudden change in the direction of the CUSUM plot indicates a shift in a mean, and a point at which the direction shifts is recognised as the change point.

Splitting the Data

The objective of segmentation is to extract intervals exhibiting unique statistical characteristics (e.g., mean or variance) as determined by CPA, so enabling independent examination of trends and variability within each segment. The dataset was partitioned at critical changepoints identified by the CUSUM. For the initial transition point (June 2008): The time series was partitioned into two halves. Prior to June 2008: Characterized by a diminishing trend in adverse event parts. second Post-June 2008: Demonstrated an escalation in variability, presumably associated with battery and device malfunctions. Regarding the second change point (May 2011): The portion following June 2008 was additionally divided. Prior to May 2011: Consistent adverse event reporting. Post-May 2011: Characterized by a significant increase in adverse occurrences, linked to the augmented utilisation of the device. Consequently, segmentation facilitates localised analysis to comprehend patterns and variability, while also aiding in the identification of change determinants, such as technical malfunctions (e.g., battery failures in 2008) or external influences (e.g., enlarged indicators in 2011). The figure depicting the division of a CUSUM plot (Figure 4 in the document) indicate the trajectory of cumulative sums prior to and subsequent to important transition points. The change point in June 2008 was designated as "1," and the point in May 2011 was designated as "2," with analysis conducted independently for each resulting segment.

Model Parameters

This section deals with the model parameters measurement in order to analyse the efficacy of the statistical approach implemented in this study for Surveillance and Device Safety in Medical device industries. The statistical approach in this study make use of change point analysis (CPA) framework where change in mean detection is performed using CUSUM model along with statistical testing via bootstrapping is performed for statistical analysis. Various parameters implemented in this study are depicted below in this section: In this research steps followed for the CUSUM are depicted below starting with the means shift model for time series data which helps to measure residual which shows a difference among observed value and a mean the CUSUM calculation for residuals are calculated iteratively by subtracting the overall mean then change point identification before test statistic where CUSUM difference is computed. The steps along with the equation of the implemented process is discussed in this section below:

Mean-Shift Model:

The time-series data Yi (where i=1,,...,, N) is modeled as Eq 11:

$$Yi = \mu + \epsilon i \qquad (11)$$

- μ: Sample mean

ϵi=Yi−μ: Residual (difference between observed value and the mean)

Cusum Calculation:

CUSUMs of residuals are calculated iteratively Eq 12:

$$Si = Si - 1 + \epsilon i \quad \ldots\ldots\ldots(12) \quad where\ So = 0 \qquad (12)$$

- Si: Cumulative sum at point i.

By construction, SN=0 because the overall mean is subtracted.

Change Point Identification

A potential change point is the location mmm where the absolute maximum CUSUM occurs Eq 13:

$$| Sm | = \left(\underset{i=0,\ldots,n}{max} \right) | Si | \qquad (13)$$

Test Statistic

The CUSUM difference is computed as Eq 14:

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$$Sdiff = Smax - Smin \quad ... \quad (14)$$

- S(max): Maximum CUSUM value.
- S(min): Minimum CUSUM value.

P-VALUE: A p-value," the probability that in accordance with a certain statistical model, a statistical average of the data would lie between the actual value and its extreme opposite," accurately reflects the data's compatibility with the null hypothesis[18][19]. If the p-value is less than the 0.05 significance level, the null hypothesis is rejected and the alternative hypothesis is accepted. Whether it's to determine the efficacy of a new treatment, the validity of a study's findings, or the appropriateness of a health technology's approval or denial by regulatory bodies, the p-value has emerged as the most utilised statistic in biomedical research. Nevertheless, there has been an increasing amount of talk in the biomedical community about how p-values and "statistical significance"—the categorisation of outcomes as "significant" or "not significant" depending on whether the p-value is below a specific threshold—are frequently misunderstood and misused, despite their usefulness[20]. The arrival of Big Bata will only make matters worse. The purpose of this piece is to bring awareness to the proper use and understanding of p-values in clinical research.

Hyper-parameters tuning is a key step to find the optimal machine learning parameters. Determining the best hyper-parameters takes a good deal of time, especially when the objective functions are costly to determine, or myriad parameters are required to be tuned.Hyper-parameters tuning is a key step to find the optimal machine learning parameters. Determining the best hyper-parameters takes a good deal of time, especially when the objective functions are costly to determine, or myriad parameters are required to be tuned

4. RESULTS AND DISCUSSION

The findings and discussion of using statistical approaches in post-market monitoring to ensure medical device safety in the healthcare industry are presented in this section. Experimental results obtained from change point analysis for post-market monitoring of neurostimulators are shown below, offering useful insights for post-market surveillance. The paragraph below presents various tables and graphs illustrating CUSUM data before 2008 and after 2009 for the purpose of monitoring findings from the statistical analysis employing change point analysis.

Experimental Results

The results portion of the study offers a detailed analysis of the findings derived from CPA applied to the post-market monitoring data for a neurostimulator. A particularly helpful technique for identifying notable shifts in the variances or means of a series of observed data is change point analysis. The identified modification sites for medicinal items might provide useful data for post-market surveillance. This section illustrates the results of the experiments conducted on the proposed CUSUM Plot and Change Points Detection. Depending on the change points, the data series were divided, as shown in Figure 4. The transition point in June 2008 is represented by the symbol "1" in Figure 4. The data was then partitioned in June 2008, and CPA was applied separately to every of the two halves. The second major shift happened in May 2011, as shown by the symbol "2" in Figure 4. There was no additional substantial change point observed after this section was further separated in May 2011 and CPA was applied. In 2006 and 2007, CPA gained three more major change points for the left section (before June 2008). Table II displays the change points identified by CUSUM for a neurostimulator data sample, along with the significance levels associated with them. The threshold for identifying statistically significant points of change was a p-value of 0.05. June 2008 was the first possible data point for a change. At a first detected changepoint in June 2008, with a p-value of less than 0.001, the preliminary CUSUM plot for the whole time series shows the CUSUM plot. This plot was incorporated in the summary of the CUSUM plot for the complete time series. In June 2009, twenty adverse occurrences were recorded, and a retrospective investigation indicates that battery failures and other device-related issues transpired during this timeframe. The results of this study stem from a retrospective analysis. In June 2008, upon identifying the transition point, the dataset was bifurcated into two unique segments: the first was the original dataset, while the second was:

- Before June 2008
- After June 2008

Now, analysing the Analysis of Segments Before and After June 2008.

Before June 2008

Here the before June 2008 shows the CUSUM trend which is steadily declining. Here, the three additional change points were detected in 2006–2007:

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- December 2006 (n = 2, p < 0.001)
- February 2007 (n = 1, p < 0.001)
- November 2007 (n = 2, p = 0.005)

These points had very low counts, which may indicate reporting sparsity rather than clinically significant trends.

After June 2008

For the period beginning after June 2008, it is initially constant, and then it begins a substantial rising trend after 2010. A p-value of 0.003 was employed to identify the second change point for the month of May 2011, and a number of adverse events that occurred was 51. In accordance with a change, the indication for the use of the device has been expanded, which has resulted in an increase in a number of adverse events that have been reported.

The two primary change points (June 2008 and May 2011) were significant and had clear explanations: June 2008: Battery and device failure issues. May 2011: Expansion of the device's usage. Additional points in 2006–2007 had low counts and may not have strong clinical relevance. While, underreporting observed between October 2009 and January, unusually low reporting occurred.

- October 2009: 2 events
- November 2009: 3 events

This can indicate issues of underreporting, a prevalent concern in adverse event reporting systems. This study proved that similar change locations in the neurostimulator adverse event dataset were found by adjusting the mean CPA techniques. The last data period before the rise in therapeutic loss numbers in May 2011 is April 2011. Since the data update occurred in both April and May 2011, the CUSUM approach utilised the start of a new segment as the change point. One key distinction between the two methods is the number of noteworthy shifts detected in 2006 and 2007 by the change in mean technique. Instead than pooling data to identify variations in relative reporting rates across items, this research use CPA methodologies to follow changes within a single product over time. With the use of CPA, the FDA may monitor the relationship between medical items (devices, vaccines, and pharmaceuticals) and adverse occurrences over time, which would be an addition to their existing signal detection efforts. These changes may have far-reaching implications for public health regulation, monitoring of adverse events, product recall operations, and regulators' ability to grasp the link between adverse occurrences and other instances involving regulated items.

CUSUM TIME SERIES BEFORE JUNE 2008

DATA	CUSUM
2000-01	0
2000-06	-5
2001-01	-10
2001-06	-13
2002-01	-15
2002-06	-17
2003-01	-19
2003-06	-20
2004-01	-22
2004-06	-23
2005-01	-25
2005-06	-27
2006-01	-26
2006-06	-15

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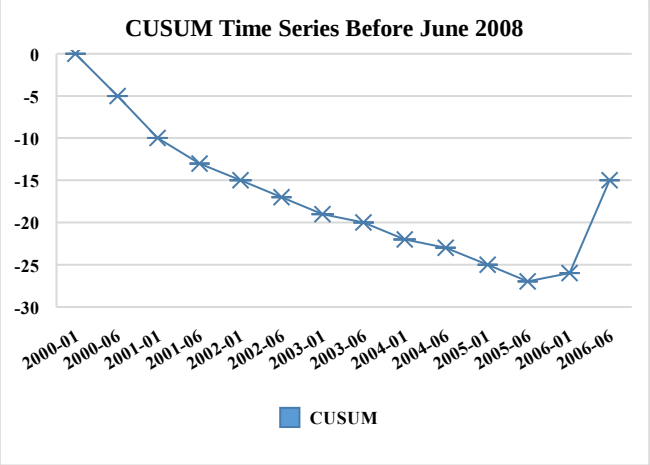

CUSUM plot for the sample neurostimulator data prior to first change point at June 2008

Table III presents the CUSUM time series data for the period before June 2008, showing the cumulative sum of adverse events over time. Starting from January 2000, the CUSUM values steadily decrease, reflecting a decline in adverse event occurrences. Notably, the values show a consistent negative trend until mid-2006, where a shift occurs with less pronounced declines, indicating a potential stabilisation in the reporting of adverse events. The CUSUM value in June 2006 is -15, a marked improvement compared to earlier years, suggesting a reduction in events or reporting frequency. Figure 5 visualises this trend, with the CUSUM plot showing a steady decline until the first significant change point in June 2008. This plot clearly highlights the gradual decline in adverse event occurrences prior to June 2008, setting the stage for the analysis of changes after this pivotal point. The consistent downward slope in the CUSUM plot before June 2008 indicates that the dataset was relatively stable in terms of adverse event occurrences before the identified change point.

CUSUM TIME SERIES AFTER JUNE 2008

DATE	CUSUM
2008-06	0
2008-09	-50
2008-12	-80
2009-03	-100
2009-06	-120
2009-09	-130
2009-12	-150
2010-03	-180
2010-06	-190
2010-09	-185
2010-12	-170
2011-03	-150
2011-06	-100
2011-09	-50
2012-01	-20

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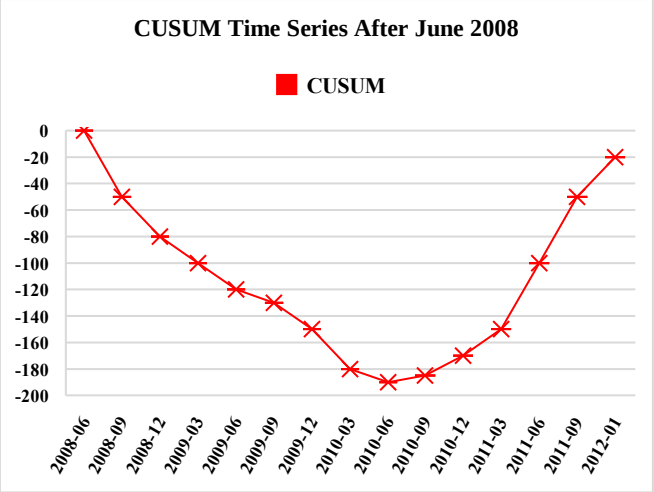
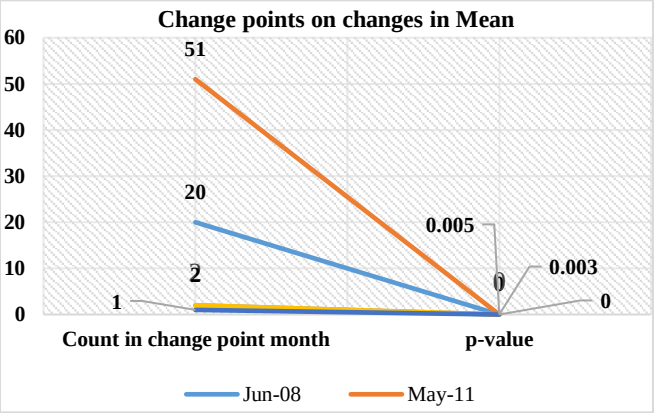


CUSUM plot for the sample neurostimulator data after first change point at June 2008

Table III presents the CUSUM time series data for the period after June 2008, showing a significant shift in the cumulative sum of adverse events. Starting at 0 in June 2008, the CUSUM values rapidly declined, reaching -50 in September 2008 and continuing to decrease until December 2009, when the cumulative sum reached its lowest point at -150. This sharp downward trend indicates a sharp increase in adverse events during this period, possibly reflecting an uptick in device-related issues or reporting. After 2010, the decline slows, and the CUSUM values show a gradual reduction to -20 by January 2012, suggesting a relative stabilization of adverse event occurrences. Figure 5 visually represents this data, with the CUSUM plot illustrating a pronounced negative slope following the June 2008 change point. The sharp drop in CUSUM following June 2008 indicates a substantial increase in adverse event reports, which could be attributed to device failures or increased usage, as noted in the study, especially in the context of the 51 adverse events recorded in May 2011. The plot clearly demonstrates the significant shift in reporting trends after the first change point, marking a notable difference from the period before June 2008.

CHANGE POINTS ON CHANGES IN MEAN

Change point	Count in change point month	p-value
June 2008	20	<0.001
May 2011	51	0.003
December 2006	2	<0.001
November 2007	2	0.005
February 2007	1	<0.001



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Sum of count in change point month by p-value

Figure 6 depicts the sum of count in change point month by p-value here x axis displays a p-value while y-axis shows the count in change point month. Table IV highlights the significant change points identified in the neurostimulator's post-market surveillance data, along with the corresponding p-values and the count of adverse events in the change point month. The most notable change point occurred in June 2008, with 20 adverse events and a p-value of <0.001, indicating a highly significant shift in the data. The second major change point is in May 2011, with 51 adverse events and a p-value of 0.003, suggesting an increase in adverse events likely due to expanded device usage. Additionally, smaller change points were identified in 2006 and 2007, with fewer adverse events (ranging from 1 to 2 events), but these were still statistically significant, with p-values <0.001 to 0.005. Figure 6 visualises the sum of counts in change point months by p-value, showing a clear concentration of significant change points (with lower p-values) around 2006–2008. This Figure 6 effectively illustrates the strong relationship between significant adverse event counts and the timing of key change points, reinforcing the role of Change Point Analysis in identifying temporal shifts in adverse event reporting. The data suggests that the most impactful changes occurred in June 2008 and May 2011, aligning with key events related to device performance and usage changes.

The results of this study highlight the effectiveness of CPA in identifying significant shifts in adverse event reporting for a neurostimulator, offering valuable insights for post-market surveillance. The analysis identified two major change points—June 2008, linked to battery and device failures, and May 2011, associated with an expansion in the device's usage. The CUSUM plot demonstrated a steady decline before June 2008, with three minor change points detected in 2006–2007, though these were likely due to reporting sparsity rather than clinical relevance. The period after June 2008 showed a rising trend, coinciding with an increase in reported adverse events following the device's expanded use. Additionally, the study revealed underreporting issues in late 2009, with significantly lower reported events. These findings underscore the utility of CPA as a supplementary tool for FDA signal detection systems, helping identify temporal variations in adverse event patterns and contributing to improved public health regulation, product recalls, and a deeper understanding of device-related risks.

5. CONCLUSION AND FUTURE SCOPE

The work highlights the need of applying robust statistical approaches, namely Change Point Analysis (CPA), in the context of PMS of medical devices. Within the framework of PMS of MD, the study highlights the significance of employing robust statistical approaches, specifically Change Point Analysis (CPA), as a means of ensuring the safety of the devices. This research demonstrates an effectiveness of CPA in enhancing post-market surveillance (PMS) for neurostimulators by identifying significant shifts in adverse event patterns over a twelve-year period (2000–2012). Using the Cumulative Sum Control Chart (CUSUM) method, two major change points were detected in June 2008 and May 2011, linked to battery failures and the expansion of device warnings, respectively. The analysis segmented the data into pre- and post-change intervals, revealing critical trends, such as underreporting and increased adverse events. Statistical validation methods, such as bootstrapping, complement CPA, making it a useful tool for identifying changes in adverse event data over time. This provides a methodical way to enhance safety monitoring, regulatory procedures, and future studies related to medical device safety. The study's limitations include the possibility of underreporting of adverse events, especially during certain time periods like late 2009, which might impact the precision of the change points that were observed. Findings may not apply to other types of medical devices due to the exclusive emphasis on neurostimulators. Future work could expand the application of CPA to a broader range of medical devices, integrate larger and more diverse datasets for enhanced statistical power, and explore advanced machine learning techniques for more nuanced detection of change points. Furthermore, refining methods to account for reporting biases and integrating real-time data could further improve the effectiveness of post-market surveillance.

REFERENCES

1. C. S. Lao, L. G. Kessler, and T. P. Gross, "Proposed statistical methods for signal detection of adverse medical device events," *Ther. Innov. Regul. Sci.*, 1997, doi: 10.1177/009286159803200126.
2. The European Parliament and the Council of the European Union, "Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products.," *Off. J. Eur. Union*, 2009.
3. ISO 13485:2016(E), "Medical devices – Quality management systems – Requirements for regulatory

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ISSN: 2277-9655
Impact Factor: 5.164
CODEN: IJESS7

purposes," 2016. [Online]. Available: https://www.bonnier.net.cn/download/d_20170812100731.pdf
4. AAMI, "Medical devices—Recognized essential principles of safety and performance of medical devices—Part 1: General essential principles and additional specific essential principles for all non-IVD medical devices and guidance on the selection of standards," in *ANSI/AAMI/ISO 16142-1:2016; Medical devices—Recognized essential principles of safety and performance of medical devices—Part 1: General essential principles and additional specific essential principles for all non-IVD medical devices and guidance on the*, 1st ed., 2016. doi: 10.2345/9781570206160.ch1.
5. S. Fatemeh, "Regulatory requirements of Medical Devices in MENA countries," 2015. [Online]. Available: https://www.dgra.de/media/pdf/studium/masterthesis/master_samadi_f.pdf
6. European Commission, "COMMISSION REGULATION (EU) 2017/752 of 28 April 2017 amending and correcting Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food," *Off. J. Eur. Union*, 2017, [Online]. Available: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0752
7. T. Botsis *et al.*, "Decision support environment for medical product safety surveillance," *J. Biomed. Inform.*, 2016, doi: 10.1016/j.jbi.2016.07.023.
8. M. Kulldorff and I. R. Silva, "Continuous post-market sequential safety surveillance with minimum events to signal," *REVSTAT-Statistical J.*, 2017.
9. D. Madigan, P. Ryan, S. Simpson, I. Zorych, and W. Dumouchel, "Bayesian Methods in Pharmacovigilance," in *Bayesian Statistics 9*, 2012. doi: 10.1093/acprof:oso/9780199694587.003.0014.
10. C. Zippel and S. Bohnet-Joschko, "Post market surveillance in the german medical device sector – current state and future perspectives," *Health Policy (New. York).*, 2017, doi: 10.1016/j.healthpol.2017.06.005.
11. I. Vlachos, D. Kalivas, and O. Panou-Diamandi, "An electronic post market surveillance system for medical devices," *Comput. Methods Programs Biomed.*, 2003, doi: 10.1016/S0169-2607(02)00060-3.
12. J. Chaudhry, C. Valli, M. Crowley, J. Haass, and P. Roberts, "POStCODE Middleware for Post-Market Surveillance of Medical Devices for Cyber Security in Medical and Healthcare Sector in Australia," in *International Symposium on Medical Information and Communication Technology, ISMICT*, 2018. doi: 10.1109/ISMICT.2018.8573695.
13. W. A. Taylor and W. A. Taylor, "Change-Point Analysis: A Powerful New Tool For Detecting Changes," *Analysis*, 2006.
14. S. N. A. M. Arif, M. F. M. Mohsin, A. A. Bakar, A. R. Hamdan, and S. M. S. Abdullah, "Change point analysis: A statistical approach to detect potential abrupt change," *J. Teknol.*, vol. 79, no. 5, pp. 147–159, 2017, doi: 10.11113/jt.v79.10388.
15. T. A. Kass-Hout *et al.*, "Application of change point analysis to daily influenza-like illness emergency department visits," *J. Am. Med. Informatics Assoc.*, 2012, doi: 10.1136/amiajnl-2011-000793.
16. M. Z. Hossain, "Bootstrapping – an introduction and its applications in statistics," no. January 2000, 2015.
17. V. V Koshti, "Cumulative sum control chart (CUSUM)," in *Introduction to Energy Essentials*, no. December 2011, Elsevier, 2011, pp. 559–568. doi: 10.1016/B978-0-323-90152-9.00016-5.
18. R. L. Wasserstein and N. A. Lazar, "The ASA's Statement on p-Values: Context, Process, and Purpose," *American Statistician*. 2016. doi: 10.1080/00031305.2016.1154108.
19. R. Nuzzo, "Scientific method: statistical errors.," *Nature*. 2014. doi: 10.1038/506150a.
20. S. Greenland *et al.*, "Statistical tests, P values, confidence intervals, and power: a guide to misinterpretations," *Eur. J. Epidemiol.*, 2016, doi: 10.1007/s10654-016-0149-3.

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